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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/695,577	10/28/2003	Edwin Raymond Chapman	960296-99004	8039

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QUARLES & BRADY LLP
411 E. WISCONSIN AVENUE, SUITE 2040
MILWAUKEE, WI 53202-4497

EXAMINER	
FORD, VANESSA L	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 11/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/695,577	CHAPMAN ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-14 and 41-67* is/are pending in the application.

4a) Of the above claim(s) *51-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-14 and 41-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This Office Action is responsive to Applicant's amendment and response filed response filed August 8, 2006. Claims 1-9 and 15-40 have been cancelled. Claims 10, 45 and 47 have been amended.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Rejections Maintained

3. The rejection of claims 47 under 35 U.S.C. 112 second paragraph is maintained for the reasons set forth on page 3, paragraph 4 of the previous Office Action.

The rejection is on the grounds that claim 47 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 47 recites " ...wherein the polypeptide is located *in vivo*. If Applicant intends that the polypeptide is *in vivo* then the ligand is also in vivo since the polypeptide is in a complex with the ligand. It is unclear as to whether Applicant is claiming an organism (e.g. rat, mouse or human) since the claim recites that the polypeptide is *in vivo*. Clarification and/or correction is required.

Applicant's Arguments

Applicant urges that it is clear that claim 47 is directed at a complex of the polypeptide and its antibody rather than an organism such as a rat, mouse or human.

Examiner Response

It is the Examiner's position that claim 47 remains indefinite even after Applicant's amendment filed August 8, 2006. It should be remembered that a claim should be able to stand alone. Claims should be definite. Applicant should not have to provide an explanation to one the skilled artisan so that they will understand the limitations recited in the claims. Correction is required. Thus, this rejection is maintained.

4. The rejection under 35 U.S.C. 112, first paragraph is maintained for claims 10-14 and 41-50 for the reasons set forth on pages 4-10, paragraph 4 of the previous Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 10-14 and 41-50 are directed to a complex of a ligand and a polypeptide wherein the polypeptide comprises an amino acid sequence that is homologous or at least 70% identical to a murine synaptotagmin II botulinum toxin serotype B binding domain at amino acid position 40 to 60 and wherein the ligand binds to the polypeptide at the amino acid sequence that is homologous or at least 70% identical to the murine synaptotagmin II BoNT/B-binding domain at amino acid position 40 to 60 with the proviso that where the polypeptide is a full length synaptotagmin, the ligand is not botulinum toxin.

The specification has not described the vast genus of complexes encompassed by the claims. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention.

To adequately describe the genus of complexes one must describe the structure of the complex. The claims indicated that the complex comprises a ligand and a polypeptide wherein the polypeptide comprises an amino acid sequence that is homologous or at least 70% identical to a murine synaptotagmin II botulinum toxin serotype B binding domain at amino acid position 40 to 60 and wherein the ligand binds to the polypeptide at the amino acid sequence that is homologous or at least 70% or (80%, or 90% or 95% as set forth in claims 11-13, respectively) identical to the murine synaptotagmin II BoNT/B-binding domain at amino acid position 40 to 60 with the proviso that where the polypeptide is a full length synaptotagmin, the ligand is not botulinum toxin. Applicant has not described the genus of claimed complexes such that the specification might reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

The instant specification has described complexes that comprise synaptotagmin II amino acids 1-267, complexes that comprise synaptotagmin II amino acids 61-267 and complexes that comprise synaptotagmin II amino acids 1-87. The instant specification does not describe a complex that comprises a ligand and a polypeptide that has at least 70% or 80% or 90% or 95%, identity to amino acid positions 40 to 60 of the BoNT/B-binding of murine synaptotagmin II.

The claims of the instant application are drawn to complexes that include ligands that are botulinum toxin fragments. See claim 45 in particular. The instant specification has not described how one would begin to choose "botulinum toxin fragments". The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of sequence(s) which can be predictably modified and which regions are critical;
- what fragments, if any, can be made which the retain the biological activity if the intact protein; and
- the specification provide no written description such that one skill in the art could determine which of the essentially infinite possible choice is likely to be successful.

The claims of the instant application are drawn to complexes that are formed *in vivo* in a mammal. See claim 47 in particular. The instant specification has not described how one of skill in the art would form the claimed complex in a mammal. The specification has not provided written support for the broad scope of the claims,

which encompass a vast number of complexes being formed *in vivo*. How does the skilled artisan form a complex that comprises a ligand and a polypeptide that has at least 70% or 80% or 90% or 95% identity to amino acid positions 40 to 60 of the BoNT/B-binding of murine synaptotagmin II *in vivo*?

Moreover, the specification does not disclose distinguishing and identifying features of a representative number of members of the genus of complex to which the claims are drawn, such as a correlation between the complex and reduced binding activity between botulinum toxin B and murine synaptotagmin II so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of complexes. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of complexes on which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus of complexes that provide reduced binding activity between botulinum toxin B and murine synaptotagmin II.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided: The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. *The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, `Written Description" Requirement (66 FR 1099-1111, January 5, 2001)* state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described

distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of complexes, the skilled artisan could not immediately recognize or distinguish members of the claimed complexes that would provide reduce binding between botulinum toxin serotype B and murine synaptotagmin II.

In view of the above, the instant specification fails to meet the written description in regards to the genus of complexes broadly claimed.

Applicant's Arguments

A) Applicant urges that the amendments to the claims have been made to address the rejection under 35 U.S.C. 112 first paragraph. Applicant urges that as amended the ligand recited in the claims is limited to a botulinum toxin serotype B or an antibody that binds to the a murine synaptotagmin II protein at amino acids 40-60 or an equivalent as defined in claim 10.

B) Applicant urges that the structure of synaptotagmin II is well known in the art and the specification provides the amino acid sequences of synaptotagmin II (SEQ ID Nos. 7, 9 and 10) for mouse, rat and human, respectively. Applicant urges that the written description requirement is met. Applicant urges that paragraph 37 of the instant specification provides that polypeptides that are at least 70%, 80%, 90% or 95% identical to amino acids 40-60 of a murine synaptotagmin II can compete with synaptotgmin II for BoNT/B binding. Applicant urges that the skilled artisan can envision amino acid sequences that are at least 70%, 80%, 90% or 95% identical to

amino acids 40-60 of a murine synaptotagmin II. Applicant urges that paragraphs 67-68, 71-73 and 77-78 of the specification provides a series of structural and functional experiments and the skilled artisan would appreciate polypeptides having 70% or higher identity to the BoNT/B binding domain will also be able to bind to BoNT/B.

C) Applicant urges that claims 10 and 45 have been amended to delete subject matter of BoNT/B fragments.

D) Applicant urges that the skilled artisan would appreciate that an antibody to the binding domain can be administered to an animal and that the antibody will bind to the receptor in vivo to form a complex. Applicant urges that a skilled artisan would appreciate that a polypeptide defined in claim 10 can be administered to an animal having C. botulinum toxin infection and the polypeptide will bind to the BoNT/B in vivo to form a complex.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed August 8, 2006 have been fully considered but they are not persuasive.

A) While the ligand recited in the amended claims may be directed to BoNT/B or an antibody against said amino acid sequence that is homologous or at least 70% identical to a murine synaptotagmin II botulinum toxin serotype B binding domain at amino acid position 40 to 60, the instant specification does not provide written description for "a polypeptide comprising an amino acid sequence that is homologous or at least 70% identical to a murine synaptotagmin II botulinum toxin serotype B binding domain at amino acid position 40 to 60. The instant specification does not provide

written description for the genus of polypeptides as claimed. It must be remember that the requirement under 35 U.S.C. 112 first paragraph written description is that Applicant must adequately describe their invention at the time of filing. Applicant has claimed a genus of polypeptides that encompasses any deletion or substitution along the polypeptide.

B) Although the amino acid sequences are know for mouse, rat and human synaptotagmin II, the instant specification (paragraphs 67-68, 71-73 and 77-78) merely states how the skilled artisan may "find" these polypeptides. There is no indication that they were in possession of these polypeptides at the time of filing. The instant specification has not adequately described the claimed invention and thus, fails to met the written description guidelines as set forth in 35 U.S.C. 112, first paragraph.

C) The Examiner disagrees with Applicant's assertion that claims 10 and 45 have been amended to delete subject matter of BoNT/B fragments. The claims as amended include fragments or amino acid sequences that are less than the full-length "synaptotagmin II". The claims as amended recite "polypeptides comprising an amino acid sequence that is homologous or at least 70% identical to a murine synaptotagmin II botulinum toxin serotype B binding domain at amino acid position 40 to 60". This genus of polypeptides include fragments. Thus, this rejection is maintained.

D) To address Applicant's comments regarding the antibodies or polypeptides of the invention may be used to bind to the receptor in vivo to form a complex", it should be noted that the Examiner is not questioning the function of the genus of polypeptides claimed, but is questioning the structure of the genus of

polypeptides (e.g. polypeptides comprising an amino acid sequence that is homologous or at least 70% identical to a murine synaptotagmin II botulinum toxin serotype B binding domain at amino acid position 40 to 60) that are encompassed by the claims. It is the Examiner's position that Applicant was not in possession of this genus of polypeptides at the time of filing.

5. The rejection under 35 U.S.C. 102(b), is maintained for claims 10-14 and 41-43 and 45-50 for the reasons set forth on pages 10-11, paragraph 6 of the previous Office Action.

The rejection was on the grounds Kozaki et al teach a complex comprising a MBP- Stg2N (maltose and synaptotagmin II fusion comprising amino acids 1-87 of the synaptotagmin II of botulinum toxin B) inhibited botulinum toxin B binding activity (page 95, 2nd column and page 97, 1st). Kozaki et al teach that when the MBP-fusions proteins were incorporated into lipid vesicles together with gangliosides, (GT1b or GD1a) a toxin bound only to MBP-Stg2N/Gt1b and MBP-stg2N/GD1a lipid vesicles indicating that MBP- Stg2N has a ganglioside binding site (page 92, 2nd column). Kozaki et al teach an antibody against GT1b effectively inhibited not only BoNT/B binding to the reconstituted lipid vesicles and brain synatosomes but also type A binding to brain synaptosomes (see the Abstract). Kozaki et al teach that polypeptide used in the complex of the prior art were recombinantly made (page 97, 1st column). Kozaki et al anticipate the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's complex with the complex of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant's Arguments

A) Applicant urges that urges that Kozaki et al teach a complex of MBP-Stg2N but do not specifically teach that in their complex BoNT/B binds to amino acids 40-60 of synaptotagmin II as required by the claims.

B) Applicant urges that Nishiki et al, FEBS Letters, 1996 teach that two antibodies used bind to amino acids 9-14 and 1-20 of synaptotagmin II.

C) Applicant urges that claim 44 recites "consists of" of the BoNT/B binding domain of synaptotagmin II and Kozaki et al cannot anticipate this claim because of the closed claim language.

Examiner's Response to Applicant's Arguments

A) The Examiner disagrees with Applicant's assertion that "Kozaki et al do not specifically teach that MBP-Stg2N binds amino acids 40-60 of synaptotagmin II". It should be noted that MBP-Stg2N includes the N-terminal domain (amino acids 1-60 of synaptotagmin II) as well as the transmembrane region (61-87 of synaptotagmin II). Kozaki et al teach that BoNT/B bound to the rat ganglioside binding domain (page 92). Kozaki et al also teach an antibody, against GT1b, 3A2 (page 93). It should be remembered that the ganglioside binding domain for rat synaptotagmin II is amino acids 53-79. Thus, the prior art teaches a polypeptide comprising an amino acid sequence

that is at least 70% identical to a murine synaptotagmin II botulinum toxin serotype B binding domain at amino acid position 40 to 60 as well as an antibody against position 40 to 60 of synaptotagmin II.

B) To address Applicant's comments regarding antibodies, it should be noted that this rejection is anticipated by Kozaki et al and not Nishiki et al. Therefore, the antibodies disclosed in Nishiki et al are not relevant. It should be remembered that Kozaki et al teach that BoNT/B recognizes the N-terminal domain (e.g. amino acids 1-60 of synaptotagmin II).

C) Claim 44 has been removed from this rejection.

Status of Claims

6. No claims allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

8. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the acting examiner's supervisor, Bruce Campell, can be reached at (571) 272-0974.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
October 22, 2006

NITA MINNIFIELD
PRIMARY EXAMINER

NITA MINNIFIELD
PRIMARY EXAMINER